CHEMICAL MANUFACTURERS ASSOCIATION

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

May 18, 1998

Dr. Kenneth Olden
Dr. C. W. Jameson
National Toxicology Program,
Report on Carcinogens
111 Alexander Drive, Bldg. 101
MD EC-14, P.O. Box 12233
Research Triangle Park, NC 27709

Re: Proposed Cancer Classification for 1,3-Butadiene

Dear Drs. Olden and Jameson:

The Chemical Manufacturers Association Olefins Panel (Panel) is submitting these comments in response to the National Toxicology Program (NTP) request for public comment on its proposal to list 1,3-butadiene as "known to be a human carcinogen" in the Report on Carcinogens, Ninth Edition. 63 Fed. Reg. 13418 (March 19, 1998). Members of the Olefins Panel include the major domestic producers and importers as well as some users of butadiene.[1]

The Panel believes the cancer classification for butadiene should not be elevated to "known." The Panel's position is supported by recent deliberations of the International Agency for Research on Cancer (IARC) and the EPA Science Advisory Board (SAB); both bodies concluded that the available data are not sufficient to elevate the cancer classification for butadiene from "probable" to "known." The Panel suggests that the assessment of butadiene should be returned to the NTP Board of Scientific Counselors Subcommittee ("NTP Board Subcommittee") for reevaluation of the available human, animal and mechanistic data before a final decision and recommendation is made.

BACKGROUND

The Panel has for many years conducted a multi-disciplinary research program to develop data that can be used to improve hazard and risk assessment for butadiene. The Panel's research has encompassed cancer and non-cancer effects, has been conducted in several different laboratories, and has been coordinated with the research efforts of other investigators around the

[1] Members of the Panel include: Asahi Chemical Industries, America; BP Chemicals, Inc.; Chevron Chemical Company; The Dow Chemical Company; DuPont; Eastman Chemical Company; Equistar Chemicals, LP; Exxon Chemical Americas; Huntsman Corporation; Occidental Chemical Corporation; Shell Chemical Company; and Union Carbide Corporation.

world. Much of the Panel's research has been published in the peer-reviewed literature. Moreover, prior to publication, the Panel has shared its research results with government agencies through annual research review meetings, three international symposia (two of which were co-sponsored by the Panel), Society of Toxicology forums and written submissions.

The Panel submitted a letter to NTP on August 22, 1997, in response to a Federal Register notice soliciting input to NTP's review of butadiene's cancer classification. The Panel urged NTP to consider information contained in two recent butadiene toxicology reviews by Himmelstein *et al.* (1997) and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997).[2] Both of these documents were provided as attachments to a separate letter submitted in August, 1997 by the International Institute of Synthetic Rubber Producers (IISRP).

NTP's Draft Background Document for 1,3 Butadiene ("Draft Background Document") was received by the Panel on October 6, 1997. The Panel submitted preliminary comments on the Draft Background Document on October 28, 1997. These comments expressed the Panel's reservations concerning NTP's tentative recommendation to elevate the cancer classification for butadiene. The Panel's comments also identified several significant errors and omissions in the Draft Background Document, including significant published studies that had not been included. For example, the discussion of the genotoxicity data omitted recent negative studies, and the discussion of pharmacokinetics omitted significant work performed at the Chemical Industry Institute of Toxicology (CIIT).

The Panel's comments were supported by a statement prepared by Dr. Richard Irons of the University of Colorado, which presented emerging evidence that the excess leukemia finding reported by Delzell *et al.* (1996)[3] may be confounded by the presence of other biologically active compounds, such as dimethyldithiocarbamate (DMDTC), which was used as the primary reaction stopper in styrene-butadiene rubber (SBR) production from approximately 1950 to 1965. Additional comments on the available human data were presented in a statement prepared by Dr. John F. Acquavella, included as an attachment to separate comments submitted by IISRP. Additionally, the Panel attended the NTP Board Subcommittee meeting on October 30, 1997, though opportunity to present oral comments was limited to five minutes.

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2 M.W. Himmelstein, *et al.* (1997). Toxicology and Epidemiology of 1,3-Butadiene. *Critical Reviews in Toxicology* 27:1-108; ECETOC (1997). *1,3-Butadiene OEL Criteria Document (Second Edition), CAS No. 106-99-0.* Special Report No. 12 (Brussels, Belgium).

3 E. Delzell *et al.* (1996). Follow-up Study of Synthetic Rubber Workers. *Toxicology* 113:182.

I. THE BUTADIENE CANCER CLASSIFICATION SHOULD NOT BE ELEVATED TO "KNOWN"

In February 1998, IARC reviewed butadiene's cancer classification and concluded that the classification should not be changed, *i.e.*, the classification should stay as "probable" and not be elevated to "known." The Panel believes NTP's cancer classification criteria, which are similar to the IARC approach, should produce the same result.

A. The Human Data Should Be Considered "Limited"

NTP's proposal to elevate the cancer classification for butadiene to "known" is based primarily on human data. *See* Draft Background Document at RC-1. The strength of the human data is addressed in the separate statement prepared by Dr. John F. Acquavella, submitted by IISRP. For reasons presented in his statement, which the Panel incorporates by reference herein, the Panel believes the human data must be considered "limited" under NTP's cancer listing criteria. Without repeating all the information presented in Dr. Acquavella's statement, a few points deserve special emphasis.

First, as explained in Dr. Acquavella's statement, only one human study can fairly be described as clearly positive.[4] That study provides evidence of an excess of leukemia only in workers involved in the SBR production process, and similar excesses have not been observed in monomer studies despite follow-up periods that approach half a century. Thus, at this point, only the SBR process has been shown to be positive for leukemia. The important element of consistency clearly is lacking in the butadiene epidemiology data. An excess of leukemia has been observed in SBR workers, but not in monomer workers.

Second, the inconsistent results between the monomer and SBR studies suggest the possibility of a confounding factor in the SBR industry. Though not addressed in the original UAB study report, the possible role of dithiocarbamates as potential confounders in the UAB study has now been documented in the peer-reviewed literature (Irons and Pyatt, 1998).[5] This

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[4] See n.3 for a citation to this study, commonly known as the University of Alabama or UAB study.

[5] Irons, R.D., and Pyatt, D.W. (1998) Carcinogenesis 19:539-542. Dithiocarbamates as potential confounders in butadiene epidemiology. *Carcinogenesis* (in press). A copy of this paper is provided with these comments as Appendix I. The authors explain that the hematotoxicity and immunotoxicity of dithiocarbamates (DTC) have been implicated in a wide range of clinical, animal and molecular studies, and they show a high concordance between the risk of developing leukemia in SBR production and opportunity for exposure to this class of agents which were used as stopping agents in the SBR process. The authors conclude, "[T]he concordance between opportunity for exposure to DTC and leukemia risk encountered in the industry, the fact that

information was expressly excluded from consideration by the NTP Board Subcommittee, because the information had not yet been published. However, the Panel believes this information, considered in combination with the clearly inconsistent results between monomer and SBR studies, precludes a finding that the human data are "sufficient" as required by NTP's cancer classification criteria. Stated differently, because the possibility of confounding cannot be excluded, the proper classification for butadiene is "reasonably anticipated to be a human carcinogen."[6]

B. Other Relevant Data Do Not Justify Elevating Butadiene's Cancer Classification

In the Draft Background Document, NTP identifies "mechanistic data" which NTP believes support classifying butadiene as a "known human carcinogen." *See id.* at RC-2. The Panel believes NTP has understated the existence and importance of species differences in metabolism of butadiene, and overstated the significance of the very limited data available regarding butadiene in human tissue and urine. The Panel believes the other relevant data are not supportive of a "known" cancer classification, and certainly are not sufficient to elevate butadiene's cancer classification, based on "limited" human data, from "probable" to "known." IARC also reached this conclusion in its February 1998 review of butadiene carcinogenicity. The other relevant data are summarized in Attachment A to this letter.

II. IARC AND THE EPA SCIENCE ADVISORY BOARD HAVE CONCLUDED THAT AVAILABLE DATA ARE NOT SUFFICIENT TO CLASSIFY BUTADIENE AS A KNOWN HUMAN CARCINOGEN

As already indicated, NTP's recommendation to elevate the cancer classification for butadiene is contradicted by the recent deliberations of IARC and the EPA SAB, both of which concluded that the cancer classification for butadiene should not be changed.

IARC evaluated butadiene very carefully over a period of several days in February, 1998. Scientists representing all relevant disciplines were included in the deliberations, and all published data was considered, including information overlooked by NTP. At the end of the process, more than half the voting members found the available data not sufficient to justify classifying butadiene as a "known" human carcinogen.

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increased leukemia incidence is encountered in SBR processing but not BD [butadiene] monomer workers, the demonstrated biological and clinical activity of DTC, together with our emerging understanding of their potent role in the modification of gene expression in immune function and hematopoiesis provide a compelling rationale for further investigation." *Id.* at 103.

6 NTP's cancer classification criteria state that the "reasonably anticipated" classification is appropriate where "alternative explanations, such as chance, bias or confounding factors, could not be adequately excluded." *See* Draft Background Document at LC-1.

The EPA SAB met for the two full days (April 30 and May 1, 1998) to review a draft risk assessment for butadiene prepared by EPA. The draft risk assessment included a proposal to classify butadiene as a "known" human carcinogen. As with IARC, scientists representing all relevant disciplines were on hand (*see* materials in Appendix II), and the latest available information was considered. The SAB deliberations also included two invited experts -- Dr. Genevieve Matanoski of Johns Hopkins University and Dr. Ronald Melnick of the National Institute of Environmental Health Sciences -- and both spoke in support of EPA's proposed cancer classification. Nevertheless, at the end of the two days, eleven of the fourteen SAB members concluded that the data do not support elevating the cancer classification for butadiene to "known".[7]

The IARC and SAB deliberations had several important advantages compared to the NTP Board Subcommittee meeting in October, 1997, including: (1) as already stated, all scientific disciplines were represented at the IARC and SAB meetings; (2) greater opportunity was provided for review of written materials, including, in the case of the SAB, written comments submitted by several interested parties; (3) many of the leading investigators involved in butadiene research were present; (4) IARC and SAB panelists had meaningful opportunities to ask questions and probe difficult scientific issues; and (5) much more time was devoted to butadiene issues, compared to the relatively abbreviated discussion permitted at the NTP meeting in October. These significant differences render the IARC and SAB assessments more credible than the NTP Board Subcommittee recommendation (which was not unanimous).

III. NTP SHOULD REEVALUATE BUTADIENE BEFORE MAKING A FINAL DECISION

The Panel believes NTP should not change butadiene's cancer classification to "known" in its Ninth Report. Instead, the assessment of butadiene should be referred back to appropriate committees for reevaluation in light of recently-published information[8] and the contrary evaluations of IARC and the EPA SAB. Reevaluation would allow NTP to correct the significant deficiencies in its Draft Background Document, none of which have been addressed thus far. Reevaluation also would enable NTP to provide a more meaningful opportunity for public comment and a better peer review -- in short, a process in which public comments are

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7 BNA, *Daily Environment Report*, May 4, 1998.

8 To the extent NTP purports to rely on mechanistic data, it is imperative that its analysis reflect all available information in that area, which clearly is not the case with the Draft Background Document for butadiene. Similarly, the paper by Irons and Pyatt (1998) provides important information that was not considered by NTP in October, 1997 because the paper was not yet published.

considered carefully and peer reviewers are given adequate time to explore in a rigorous manner the important scientific issues.

Butadiene currently is classified by NTP as a compound that is "reasonably anticipated to be a human carcinogen." That is a significant statement, analogous to IARC or EPA classifying a compound as a "probable human carcinogen." Chemicals that receive such a classification typically are handled as if they pose a human cancer risk, such that raising the classification to "known" is unlikely to have a significant impact on risk management activities. On the other hand, prematurely elevating a cancer classification to "known" in the presence of important scientific uncertainties, as exist in the case of butadiene, undermines the objectivity of the chemical review process. The Panel believes elevating the cancer classification for butadiene is not scientifically appropriate based on all the available data, and urges NTP to reconsider its recommendation.

The Panel appreciates this opportunity to comment on NTP's review of butadiene. If you have any questions, please call Dr. Elizabeth J. Moran, Manager of the Olefins Panel, at (703) 741-5617.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

cc: Larry G. Hart, Executive Secretary

ATTACHMENT A

Other Relevant Data Do Not Justify Elevating Butadiene's Cancer Classification

In the Draft Background Document for butadiene, NTP identifies "mechanistic data" which the NTP believes support classifying butadiene as a "known human carcinogen". *See* Draft Background Document at RC-2. NTP has understated the existence and importance of species differences in metabolism of butadiene, and overstated the significance of the very limited data available in human tissue and urine. The Panel believes the other relevant data are not supportive of a "known" cancer classification, and certainly are not sufficient to elevate butadiene's cancer classification, based on "limited" human data, from "probable" to "known". IARC also reached this conclusion in its February 1998 review of butadiene carcinogenicity.

First, major quantitative differences in metabolite formation exist between species. The mouse forms more reactive metabolites and those formed persist longer than is the case for humans.

In vitro and *in vivo* data clearly show the initial oxidation of butadiene to 1,2-epoxy-3-butene (EB) is faster in mice compared to rat or human (*see* review by Himmelstein *et al.*, 1997). In the mouse, EB is further oxidized directly through cytochrome P450 IIEI to 1,2:3,4-diepoxybutane (diepoxide or DEB), in part because EB is thought to bind more tightly to mouse CYP2EI, due to the particular molecular configuration in that species (Lewis *et al.*, 1997). EB also is eliminated by glutathione conjugation and epoxide hydrolysis, and *in vitro* and *in vivo* data show that glutathione conjugation is the predominant pathway in the mouse (Csanady *et al.*, 1992; Sabourin *et al.*, 1992; Sharer *et al.*, 1992; Nauhaus *et al.*, 1996). Mice have much less epoxide hydrolase activity compared to rats or humans (Csanady *et al.*, 1992; Krause *et al.*, 1997).

In the human, the formation of EB is slower than in mice (Csanady *et al.*, 1992). Further oxidation of EB to DEB is also slower in humans than mice based on data from isolated rodent and human cell preparations (microsomes) (Csanady *et al.*, 1992; Seaton *et al.*, 1995; Krause and Elfarra, 1997). The predominant pathway for elimination of EB in humans is by epoxide hydrolysis to form butenediol and subsequent conjugation with glutathione and excretion in the urine as the mercapturic acid MI [1,2-dihydroxy-4-(N-acetylcysteinyl)-butane] (Bechtold *et al.*, 1994). (M1 is synonymous with N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine, as reported by Nauhaus *et al.* (1996)).

While DEB is produced in isolated human cell preparations, there is no evidence that the diepoxide or metabolites of the diepoxide are formed in humans. Even if DEB

were formed in humans, it would be readily eliminated by epoxide hydrolysis (Boogaard *et al.*, 1996; Boogaard and Bond, 1996). Although both diepoxide and butenediol can go on to form epoxybutanediol as suggested by in vitro studies (Cheng and Ruth, 1993; Boogaard and Bond, 1996), the weight of evidence indicates that this occurs in humans by way of EB to butenediol to epoxybutanediol. This pathway is consistent with the recent quantitation of the epoxybutanediol hemoglobin adduct, N-(2,3,4-trihydroxybutyl) valine in humans occupationally exposed to approximately 1 ppm butadiene (Perez *et al.*, 1997).

These differences in metabolites are important to consider since it is the metabolites, and not butadiene itself, which are biologically active. The diepoxide is an important metabolite in the mouse in this regard, since it has been shown to be 100 times more potent than the monoepoxide in causing genetic changes in rodents (Cochrane and Skopek, 1994). Diepoxide levels in mice are 40 to 100 times higher than in rats (Thornton-Manning *et al.*, 1995). There is no evidence that diepoxide is formed in butadiene-exposed workers.

Second, studies of cytogenetic or mutagenic changes in the blood of exposed workers are negative, equivocal, or inconsistent. The cytogenetic changes which could be expected to occur with DEB have not been seen in humans (Sorsa *et al.*, 1996). *Hprt* is a nonspecific marker of gene alteration. The elevation reported by Ward *et al.* (1994; 1996) has not been confirmed in another worker population using a different assay methodology (Tates *et al.*, 1996). Further studies are in progress (through collaboration of HEI, CEFIC, CMA and IISRP) to resolve this apparent discrepancy.

Third, butadiene metabolites have not been shown to cause changes in human bone marrow that would be expected if they could cause leukemia. Although the butadiene epoxides show evidence of carcinogenicity in the rodent, Irons *et al.* (1996) have shown that the T-cell lymphoma response in mice is due to deactivation by EB of a specific population of stem cells in the mouse bone marrow. This cell population is not present in the human or rat bone marrow. Further, Irons *et al.* have shown that EB and DEB show no toxicity for human or rat bone marrow stem cells.

There is no evidence that DEB would cause leukemia in man even if present. In fact, DEB is an active metabolite of Treosulfan, a chemotherapeutic agent that is used to treat ovarian cancer in humans. A second chemotherapeutic agent, Myleran, does not produce DEB as a metabolite. Both agents are associated with secondary acute mylogenous leukemia, arguing against DEB as the causative agent. Ashby (1993) has proposed that the leukemogenesis is due to the presence of the sulfonium moiety present in both Treosulfan and Myleran, not to the DEB.

The only reason for the possible inference that butadiene metabolites are associated with leukemia is through the increase in leukemia seen in SBR workers associated with butadiene exposure, as no such increase is seen in the butadiene monomer industry. As already noted, it has been found that the leukemia incidence in the SBR studies appears to correlate with the use of a stopping agent -- sodium dimethyl dithiocarbamate (DMDTC) -- with the highest leukemia increase seen with predicted higher coexposures. Available data show that DMDTC has a potent effect on hematopoiesis and the immune system (Irons and Pyatt, 1998).

The Panel is following up on these indications that DMDTC may be a confounder in butadiene epidemiology studies by sponsoring further research. Dr. Irons is conducting a research program to further characterize the significance of DMDTC-induced bone marrow toxicity on hematopoietic stem cell differentiation and leukemogenesis. Dr. Macaluso, at the University of Alabama, is developing estimates of worker exposure to DMDTC in the SBR workplace, using methodology similar to that used by him to estimate butadiene and styrene exposure in the SBR workplace for the UAB study.

Hence, the Panel concludes the available mechanistic and associated data do not support that butadiene is a human carcinogen, and indicate that the leukemia seen in SBR workers could be the result of a confounding exposure. Thus, there is no scientific basis for elevating butadiene's cancer classification above "probable", which is the proper classification under NTP's criteria where, as here, the animal data are "sufficient" and human data are "limited".

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APPENDIX I

IRONS AND PYATT (1998)

Due to copyright infringement laws the attached commentary could not be displayed. Please refer to the following citation:

Irons, R.D., and Pyatt, D.W. (1998). Dithiocarbamates as potential confounders in butadiene epidemiology. Carcinogenesis 19:539.

Report on Carcinogens Group

APPENDIX II

ROSTER AND AGENDA
SCIENCE ADVISORY BOARD 1,3-BUTADIENE REVIEW

U.S. ENVIRONMENTAL PROTECTION AGENCY
Science Advisory Board
Environmental Health Committee
1,3-Butadiene Review
April 30 - May 1, 1998
401 M. Street, S.W., North Conference Room 3, Washington, DC

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Acting Designated Federal Official

Ms. Roslyn A. Edson, U. S. Environmental Protection Agency
Science Advisory Board (1400), 401 M Street, SW, Room 2812M
Washington, DC 20460,(202) 260-8414,(202) 260-7118 (FAX)

Designated Federal Official

Mr. Samuel Rondberg
(Will not be participating in this review)

Staff Secretary

Ms. Mary L. Winston, Environmental Protection Agency
Science Advisory Board (1400), Washington, DC 20460
(202) 260-2554,(202) 260-7118 (FAX)

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April 28, 1998, 1:32 p.m.

U.S. ENVIRONMENTAL PROTECTION AGENCY
Science Advisory Board
Environmental Health Committee
Agenda for 1,3-Butadiene Review
April 30 - May 1, 1998
401 M Street, S.W., Washington Information Center Conference Room North 3,
Washington, D.C. 20460

DAY 1/APRIL 30, 1998

9:00 a.m. - 9:30 a.m.	-	Introduction of New Co-Chair, (Dr. Utell) Acting Designated Federal Officer (Ms. Edson), New Members (Dr. Bearer, Dr. Hoel and Dr. Doull), and Invited Experts (Dr. Matanoski and Dr. Melnick) Public Disclosures
9:30 a.m. - 10:20 a.m.	-	Agency Briefing on 1,3-Butadiene Health Risk Assessment Vanessa Vu, Associate Director for Health Aparna M. Koppikar, Epidemiologist National Center for Environmental Assessment
10:20 a.m. - 10:40 a.m.	-	James Bond, CIIT Summary of IARC Working Group Evaluation of 1,3-Butadiene
10:40 a.m. - 10:50 a.m.	-	Ronald Melnick, NIEHS Summary of NTP Evaluation
10:50 a.m. - 11:00 a.m.	-	Bette Meek, Health Canada Summary of Health Canada Evaluation
11:00 a.m. - 11:10 a.m.	-	Adam Finkel, OSHA Summary of OSHA 1,3-Butadiene Standard
11:10 a.m. - 11:20 a.m.	-	**BREAK**
11:20 a.m. - 12:00 p.m.	-	Public Comments (Please see attached list of speakers)
12:00 p.m. - 1:00 p.m.	-	**LUNCH**
1:00 p.m. - 2:00 p.m.	-	Continuation of Public Comments

(Continued on back of page.)

April 28, 1998, 1:32 p.m.

DAY 1/APRIL 30, 1998 (Continued)

2:00 p.m. - 5:00 p.m.	-	Response to the Charge The Charge questions will be addressed by reviewing the document chapter by chapter (See Attached Charge)
2:00 p.m. - 2:10 p.m.	-	Chapter 1: Introduction **(Dr. Utell)**
2:10 p.m. - 2:30 p.m.	-	Chapter 2: Exposure **(Dr. Li, Dr. Parkinson)**
2:30 p.m. - 4:00 p.m.	-	Chapter 7: Epidemiology **(Dr. Hoel, Dr. Lewis, Dr. Shore)**
4:00 p.m. - 5:00 p.m.	-	Chapter 5: Reproductive-Developmental Toxicology **(Dr. Faustman, Dr. Bearer)**

April 28, 1998, 1:32 p.m.

U.S. ENVIRONMENTAL PROTECTION AGENCY
Science Advisory Board
Environmental Health Committee
Agenda for 1,3-Butadiene Review
April 30 - May 1, 1998
401 M Street, S.W., Washington Information Center Conference Room North 3.
Washington, D.C. 20460

DAY 2/MAY 1, 1998

8:30 a.m. - 8:45 a.m.	-	Summary of Charge Responses from Day 1 **(Dr. Utell)**
8:45 a.m. - 9:00 a.m.	-	Additional Public Comment
9:00 a.m. - 9:20 p.m.	-	Chapter 3: Metabolism and Pharmacokinetics **(Dr. Swenberg, Dr. Medinsky)**
9:20 a.m. - 9:40 a.m.	-	Chapter 4: Mutagenicity **(Dr. MacGregor, Dr. Kelsey, Dr. Albertini)**
9:40 a.m. - 10:00 a.m.	-	Chapter 6: Animal Toxicity **(Dr. MacGregor, Dr. Doull)**
10:00 a.m. - 10:15 a.m.	-	Chapter 8: Pharmacokinetic Modeling **(Dr. Swenberg, Dr. Medinsky)**
10:15 a.m. - 10:30 a.m.	-	**BREAK**
10:30 a.m. - 11:00 a.m.	-	Chapter 9: Quantitative Risk Assessment **(Dr. Zeise, Dr. Hoel)**
11:00 a.m. - 11:30 a.m.	-	Chapter 10: Weight of Evidence **(Dr. Zeise, Dr. Hoel)**
11:30 a.m. - 12:30 p.m.	-	Chapter 11: Risk Characterization **(Dr. Doull, Dr. Li)**
12:30 p.m. - 1:30 p.m.	-	**LUNCH**
1:30 p.m. - 1:45 p.m.	-	Discussion of Process for Developing Draft Report **(Dr. Utell)**
1:45 p.m. - 4:15 p.m.	-	Begin Preparation of Working Document

April 28, 1998, 1:32 p.m.

Speakers for Public Comments - EHC 1,3-Butadiene Review
April 30 - May 1, 1998

Speakers Scheduled for April 30, 1998

Name	Affiliation
Dr. John Acquavella	Monsanto International Institute of Synthetic Rubber Producers, Inc.
James A. Bond, Ph.D., Cancer Program Manager	Chemical Industry Institute of Toxicology
Dr. Gary Van Gelder Chair of the Butadiene Risk Assessment Work Group of the Olefins Panel	Chemical Manufacturers Association
Dr. Richard Paul	American Automobile Manufacturers Association
Dr. Santos-Burgoa, M.D., M.P.H., Ph.D., President and General Director	Instituto de Salud Ambiente y Trabajo S.C.
Richard H. Reitz, PhD, DABT	RHR Toxicology Consulting
Robert L. Sielken, Jr.,	Shell Chemical Company

Speaker Scheduled for May 1, 1998

Richard Irons, Ph.D., D.A.B.T.	Molecular Toxicology and Environmental Health Sciences Program University of Colorado Health Sciences Center, School of Pharmacy

HEALTH RISK ASSESSMENT OF 1,3-BUTADIENE
CHARGE AND ASSIGNMENTS

ORD published its first risk assessment of 1,3-Butadiene in 1985. The first document covered cancer and mutagenicity and was prepared in response to a request from the Office of Air Quality Planning and Standards to support the classification of 1,3-Butadiene as a Hazardous Air Pollutant. The recently published 1,3-Butadiene draft document was written in response to a request from the Agency's Office of Mobile Sources. The final document will be used to support a future Air Toxics Rule. This document focuses on mutagenicity, carcinogenicity, and reproductive/developmental effects. The 1,3-Butadiene document which will be reviewed at the April 30-May 1 meeting presents the Agency's first benchmark dose analysis for reproductive/developmental factors. The review document includes many new studies which have been published since 1985. This new information has changed the weight of evidence for cancer. In addition, there are exposure data available in an occupational study which is used to derive the cancer slope factor. The review document is not intended to be a comprehensive health assessment. It contains an overview of the ambient exposure and exposure to populations adjacent to emissions sources, without any actual exposure assessment as such.

The Agency is interested in comments on each of the following aspects of the document. in addition to any other comments the review group may have:

1. *Review the health risk assessment for technical quality, comprehensiveness and clarity (Address each chapter, but with specific reference to Charges 2,3, and 4).*
   Please note that the first name listed is that of the Lead Discussant and any additional names are the Co-Discussants.

Chapter 1:	Introduction **(Dr. Pfitzer, Dr. Utell)**
Chapter 2:	Exposure **(Dr. Li, Dr. Parkinson)**
Chapter 3:	Metabolism and Pharmacokinetics **(Dr. Swenberg, Dr. Medinsky)**
Chapter 4:	Mutagenicity **(Dr. MacGregor, Dr. Kelsey, Dr. Albertini)**
Chapter 5:	Reproductive-Developmental Toxicology **(Dr. Faustman, Dr. Bearer)**
Chapter 6:	Animal Toxicity **(Dr. MacGregor, Dr. Doull)**
Chapter 7:	Epidemiology **(Dr. Hoel, Dr. Lewis, Dr. Shore)**
Chapter 8:	Pharmacokinetic Modeling **(Dr. Swenberg, Dr. Medinsky)**
Chapter 9:	Quantitative Risk Assessment **(Dr. Zeise, Dr. Hoel)**
Chapter 10:	Weight of Evidence **(Dr. Zeise, Dr. Hoel)**
Chapter 11:	Risk Characterization **(Dr. Doull, Dr. Li)**

2. *Does the science support the classification of "known" human carcinogen?*

3. *Are the approaches taken to characterize plausible cancer risks reasonable given the science?*

4. *Are the conclusions and quantitative estimations for reproductive/developmental effects adequately supported?*